REMARKS

The Office Action has rejected Claims 30-33 under 35 U.S.C. §112, first paragraph, for allegedly being non-enabling. Moreover, Claims 30-31 and 34-35 are rejected under 35 U.S.C. §112, first paragraph, for allegedly being non-enabling. Claims 30-31 and 34-35 are rejected in four separate rejections under 35 U.S.C. §102(b) as defining subject matter, which allegedly is anticipated by the teachings in U.S. Patent No. 3,682,927 to Carissimi ("Carissimi"), Zouhiri, Kacens and Vaidya, respectively. Finally, Claims 32-33 are rejected under 35 U.S.C. §103(a) as defining subject matter which is allegedly rendered obvious over the teachings in Carissimi.

Applicants have amended the claims and are submitting two Declarations, a Declaration by Robert Cherny and a Declaration of Kevin Barnharn, which, when considered with the comments herein, are deemed to place the present case in condition for allowance. Favorable action is respectfully required.

At the outset, before addressing the issues, applicants wish to thank Examiner Seaman for the courtesy extended to applicants' representative at the personal interview conducted at the USPTO on June 25, 2008 and for her helpful suggestions. At the interview, all of the issues raised in the Office Action were raised. With respect to the first rejection under 35 U.S.C. §112, first paragraph, Examiner Seaman alleged that the specification does not provide enablement for the solvates and hydrates. Although admitting that one of ordinary skill in the art could have made the hydrate and solvate of the claimed compounds without undue experimentation at the time of the filing the instant application, Examiner Seaman requested that applicants prepare a hydrate/solvate to support enablement. Examiner Seaman indicated that this submission would overcome this rejection. With respect to the second enablement rejection,

Examiner Seaman indicated that the definition in Claim 30 on Page 4, Lines 2-3 of the instant specification, provides sufficient enablement for compounds wherein R^3 and $R^{'}$ are other than H and has agreed to withdraw this rejection. With respect to the '102 rejections, it was agreed that restricting R^2 to optionally substituted phenyl, optionally substituted naphthyl, optionally substituted tetrahydronaphthyl and optionally substituted biphenyl and optionally substituted heterocyclyl; COR^6; CSR^6; CN; $(CH_2)NR^9R^{10}$; $HCNOR^9$; $HCNNR^9R^{10}$; OR^{11}; SR^{11}; $NR^{11}R^{12}$ or $SO_2NR^{13}R^{14}$ would overcome the '102 rejections. With respect to the '103 rejection, Examiner Seaman indicated that the only compounds in the rejected claims for which the cited art is relevant are PBT 1051 and PBT 1033 and that the ionophore data, if presented in a Declaration, would overcome the rejection.

Applicants, in this Response, have effected the amendments referred to hereinabove as well as others. For example Claim 30, as amended, does not recite hydrate or solvate; that subject matter was not abandoned, but is recited in Claims 36 and 37. In addition in Claim 30, R^2 was amended to delete optionally substituted C_{2-6} alkenyl, and aryl is defined as phenyl, biphenyl, naphthyl and tetrahydronaphthyl. Support for the definition of aryl is found on Page 24, Lines 2-6 of the instant specification. In Claim 31, aryl was again defined as in Claim 30. Claims 32 and 33 were amended to delete hydrates and solvates, which were added as new Claims 38-41, respectively.

No new matter is added to the application.

Pursuant to the rejection of Claims 30-33 under 35 U.S.C. §112, first paragraph, the Office Action alleges that the application is not enabling for making solvates and hydrates. Further, the Office Action alleges that there is no evidence that solvates or hydrates exist.

Contrary to the allegations of the Office Action, applicants respectfully submit that the application is enabling with respect to hydrates/solvates. The preparation of hydrates/solvates was routine to one or ordinary skill in the art at the time of the filing of the instant specification. As evidence thereof, applicants are submitting a Declaration of Kevin Barnham ("Barnham Declaration"), in which the declarant so testifies and provides two examples of hydrates that were prepared in accordance with procedures that were routine to one of ordinary skill in the art at the time of the filing of the underlying application. Attention is directed to Paragraphs 6-10 in which the declarant makes a hydrate of an exemplary compound of the present invention, a compound designated as 1033. As shown by Exhibit 2, attached to the Barnham Declaration, the first hydrate that was prepared contained a 1:1 molar ratio of 1033 and water for which the hydrogen atoms of the water molecules hydrogen bond with the quinoline nitrogen and the 8-hydroxy group and the amine moiety at positions 2 and 8 of the hydroxyquinoline. The declarant also made a second hydrate, a hemihydrate of 1033, which is described in Paragraphs 11-13 of the Barnham Declaration, in which there are two molecules of 1033 per one molecule of water. (See also Exhibits 3 and 4 attached to Barnham Declaration). As testified by Dr. Barnham, as expected, the hydrogen atoms of the water molecules hydrogen bonded with the nitrogen atom of the quinoline, and the 8-OH group and the amine moiety, at the 2-position (See Paragraph 14 of Barnham Declaration). Dr. Barnham testified that the preparation of the hydrate of 8-hydroxy compounds was routine to one of ordinary skill in the art at the time of the filing of the application and that hydrates were known at the time of the filing of the application. See Paragraph 15 of Barnham Declaration. Further, Dr. Barnham testifies that the preparation of hydrates also illustrates the preparation of solvates since water is a solvent (See Paragraph 16 of Barnham Declaration) and that the preparation of other solvates of 8-

hydroxyquinolines in general was known to one of ordinary skill in the art at the time of the filing of the application (See Paragraph 17 of Barnham Declaration). To illustrate this, Dr. Barnham refers to three articles showing that various solvates of known solvents, e.g., water, DMSO and ethanol, can be formed between the polar atoms of the solvent and the nitrogen atoms and the hydroxyl group on the 8-hydroxy-quinoline (See Paragraphs 18-21 of Barnham Declaration). Thus, as testified by Dr. Barnham, at the time of the filing of the instant application, one of ordinary skill in the art had the wherewithal to prepare solvates including hydrates (See Paragraph 22) and that using the techniques known to the skilled artisan, it would have been routine to prepare solvates of the 8-hydroxyquinoline molecules of the present invention (See Paragraph 23 of Barnham Declaration).

Thus, contrary to the allegations of the Office Action, hydrates/solvates are enabled in the above-identified application. Withdrawal of this rejection is respectfully requested.

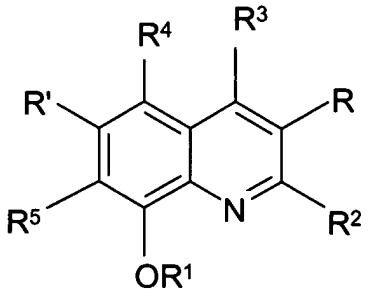
Pursuant to the second rejection under 35 U.S.C. §112, first paragraph, the Office Action alleges that the specification is non-enabling for making compounds where R^3 and R^2 are substituted heterocyclyl. More specifically, the Office Action alleges that the term "substituted" is not defined in the claims as it relates to heterocycles and concludes that one or ordinary skill will not be able to make and use the invention commensurate in scope with the claims. However, contrary to the allegations of the Office Action, this term is defined. See the last two lines of Claim 30, wherein the substituents are defined as C_{1-6}alkyl CF_3, fluorine, chlorine, iodine, cyano, C_{1-6} alkoxy, 5 or 6-membered aryl, heteroaryl, amino or C_{1-6} alkylamino.

Thus, since the substituuents are identified, it was routine for one of ordinary skill in the art to make the compounds and thus use the compounds of the present invention at the

time of the filing of the application in accordance with the teachings in the present application. The United States Patent and Trademark Office ("USPTO") concurs as indicated in the Examiner Interview Summary. Thus, this rejection is obviated; withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 30-31 and 34-35, under 35 U.S.C. §102(a), the Office Action cites various references.

The present invention is directed to, inter alia, a compound of the formula:



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or pharmaceutically acceptable salts thereof in which

R^1 is H;

R^2 is optionally substituted phenyl; optionally substituted naphthyl; optionally substituted tetrahydronaphthyl; optionally substituted biphenyl; optionally substituted heterocyclyl; COR^6; CSR^6; CN; $(CH_2)NR^9R^{10}$; $HCNOR^9$; $HCNNR^9R^{10}$; OR^{11}; SR^{11}; $NR^{11}R^{12}$ or $SO_2NR^{13}R^{14}$;

R^6 is H, C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, hydroxy, optionally substituted aryl, optionally substituted heterocyclyl, SR^7 or NR^7R^8;

R^7 and R^8 are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl and optionally substituted heterocyclyl;

R^9 is H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted heterocyclyl;

R^{10} is hydrogen, methyl, propyl, isopropyl , butyl, isobutyl, sec-butyl, tert-butyl, neopentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted heterocyclyl;

R^{11} is H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted heterocyclyl or together with R^{12} form optionally substituted heterocyclyl;

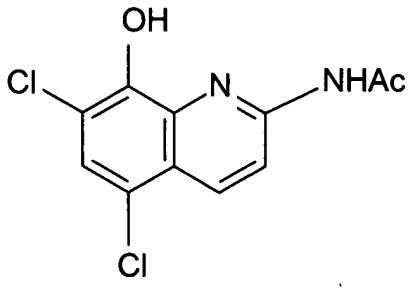
R^{12} is optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted aryl or optionally substituted heterocyclyl or together with R^{11} form optionally substituted heterocyclyl;

R^3, R and R' are either the same or different and selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{1-6} alkoxy, optionally substituted acyl, hydroxy, optionally substituted amino, optionally substituted thio, optionally substituted sulphonyl, optionally substituted sulphinyl, optionally substituted sulphonylamino, halo, SO_3H, amine, CN, CF_3, optionally substituted aryl and optionally substituted heterocyclyl; and

R^4 and R^5 are chloro,

wherein the optional substituent is C_{1-6} alkyl, CF_3, fluorine, chlorine, iodine, cyano, C_{1-6} alkoxy, 5 or 6-membered aryl, heteroaryl, amino or C_{1-6} alkylamino.

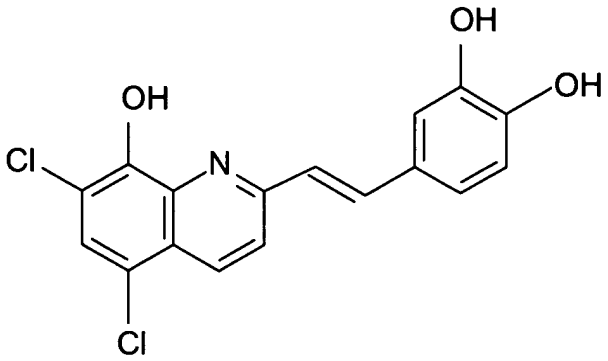
The Office Action cites Carissimi for its teaching of a compound of the following formula:



There are differences between the compounds of the present invention and the compound disclosed in Carissimi. For example, at the 2-position of the 8-hydroxyquinoline compound in Carissimi, there is an amide, $-NHC(=O)-CH_3$, wherein the amino moiety (NH) thereof is attached to the ring. On the other hand, the 2-position of the compounds of the present invention, which is the position held by R^2 does not have an amide moiety. More specifically, the compounds of the present invention are optionally substituted phenyl; optionally substituted naphthyl; optionally substituted tetrahydronaphthyl; optionally substituted biphenyl; optionally substituted heterocyclyl; COR^6; CSR^6; CN; $(CH_2)NR^9R^{10}$; $HCNOR^9$; $HCNNR^9R^{10}$; OR^{11}; SR^{11}; $NR^{11}R^{12}$ or $SO_2NR^{13}R^{14}$. Only, one of the substituents for R^2 listed hereinabove has a nitrogen atom attached to the quinoline ring, namely $NR^{11}R^{12}$. However, as defined, neither R^{11} nor R^{12} are an

acyl group (C=O). More specifically, R^{11} and R^{12} are independently, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted aryl or optionally substituted heterocyclyl or together form an optionally substituted heterocyclyl. Consequently, the compounds of the present invention cannot have a NHAc moiety at the 2- position, a position with which Examiner Seaman agrees (See Interview Summary). Thus, as defined, Carissimi does not anticipate the claimed subject matter; withdrawal of this '102 rejection is respectfully requested.

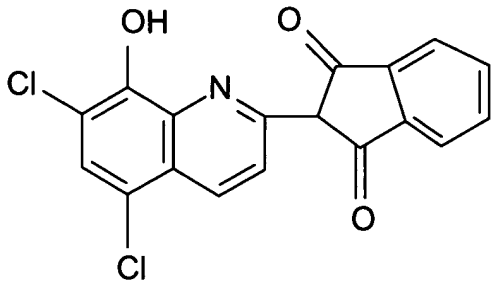
Zouhiri, according to the Office Action, disclose a compound of the formula:



In other words, the 2-position of the compound is a substituted alkenyl.

Again, there are differences between the compound in Zouhiri and the compounds of the present invention. As defined, the 2-position of the 8-hydroxyquinoline compounds of the present invention is substituted by a R^2 substituent and R^2, as defined, does not include alkenyl (or optionally substituted alkenyl). Inasmuch as R^2 is not optionally substituted alkenyl, Zouhiri cannot anticipate the compounds of the present invention, a position with which Examiner Seaman concurs (See Interview Summary Record) Therefore, the rejection of the claims under 35 U.S.C. §102(b) over Zouhiri is overcome; withdrawal thereof is respectfully requested.

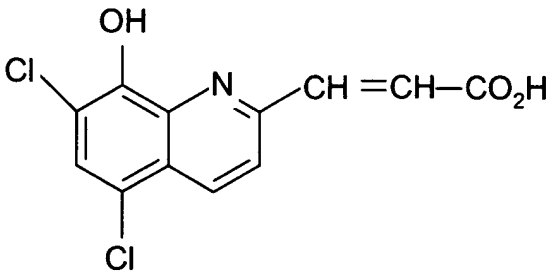
Kacens, according to the Office Action, teaches compounds of the formula:



In other words, the substituent at the 2-position is 1-indene-1,3-dione.

Again, there are differences between the compounds of the present invention and Kacens. For example, as shown hereinbelow, the 2-position of the compound in Kacens is substituted by an indene-1,3-dione. On the other hand, the 2-position of the 8-hydroxyquinoline compounds of the present invention do not contain an indene - let alone an indene -1,3-dione. Thus, Kacens does not contemplate the present invention, a position with which Examiner Seaman concurs (See Interview Summary Record). Thus, this rejection is obviated; withdrawal thereof is respectfully requested.

According to the Office Action, Vaidya teaches a compound of the following formula:



that is, an alkenyl substituent at the 2-position of the 8-hydroxyquinoline.

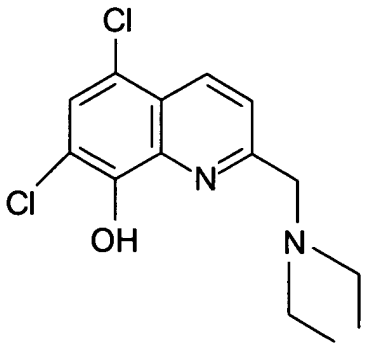
There are differences between the compounds of the present invention and the compound disclosed in Vaidya. As defined, the 2-position of the 8-hydroxyquinoline compounds

of the present invention does not contain an alkenyl moiety. Thus, Vaidya does not teach or disclose compounds of the present invention, a position with which Examiner Seaman concurs (See Interview Summary Record). Thus, this rejection is obviated; withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 32 and 33, under 35 U.S.C. §103(a), the Office Action cites Carissimi. According to the Office Action, Carissimi teaches compounds "such as shown above that differ from the instantly claimed compounds by the R^2 moiety being $-CH_2-N-Et_2$ when compounds instantly claimed have R^2 being $-CH_2-N-Me_2$ or $-CH_2-N(H)-Et$." According to the Office Action, it would have been "obvious to one of ordinary skill in the art at the time of the invention to change the diethyl for monoethyl or dimethyl with the reasonable expectation of getting compounds having the same or similar activity."

A review of the compounds recited in Claims 32 and 33 show that there are two compounds having R^2 defined as $-CH_2-N-Me_2$ and as $-CH_2-N(H)-Et$, they are 1033 and 1051, respectively. The Office Action is applying the teachings in Carissimi to reject these two compounds. According to the Office Action, Carissimi does render obvious the other compounds recited in Claims 32 and 33.

Applicants respectfully disagree that Carissimi renders obvious PBT 1033 and PBT 1051. More specifically, besides the structural differences noted hereinabove in the Office Action, there are factual and significant differences in the activity and function of PBT 1033 and PBT 1051 from the Carissimi compound referred to hereinabove. In support thereof, attention is directed to the Cherny Declaration ("Cherny Declaration"). In the Declaration, Cherny testifies on the comparison of the Carissimi compound referred to in the Office Action, namely,

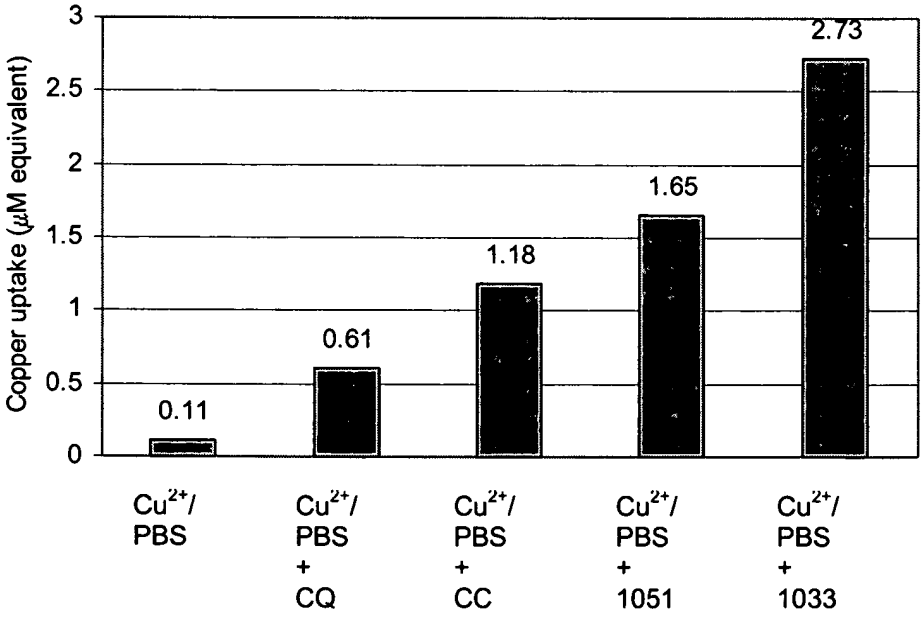


CC

hereof to referred to as the "CC" compound with 1033 and 1051. More specifically, he compared the results of the CC compound and 1051 and 1053 in an ionophore test.

To understand the ionophore test, a slight digression is required. As testified by Dr. Cherny in Paragraphs 10-14, one of the hallmarks of Alzheimer's disease is the build up the protein Abeta in the brain, forming dense insoluble, aggregates known as plaques. Abeta has been shown to be toxic to neurons and can impede normal nerve transmission, which can result in cognitive impairment and other symptoms associated with Alzheimer's disease. Current therapies in development for the treatment of Alzheimer's disease include those that are aimed at reducing the levels of Abeta in the brain. One method for reducing the amounts of Abeta in the brain is to use a compound having ionophoric properties, which is the ability to transport metal ions across the membrane into a cell, such as a neuronal cell. As testified by Dr. Cherny in Paragraph 13, there is a substantial body of literature that evidences that the amyloid precursor protein ("APP") which produces Abeta, has its expression and cleavage altered by metal ions, such as copper. Dr. Cherny further cites that the ionophoric property of a compound may influence levels of Abeta in the brain by accelerating the breakdown of Abeta after it is produced (See Paragraph 14 of Cherny Declaration). Dr. Cherny refers to a paper by White et al., attached

as Exhibit 3 to the Declaration, which shows that the use of clioquinol ("CQ") to deliver copper to cells expressing APP results in the level of Abeta in the culture medium to become dramatically reduced. As further testified, according to the paper, the presence of copper in the culture medium is insufficient to reduce the level of Abeta of itself relative to controls, and it is the ionophoric property of CQ that is required to deliver the metal across the cell membrane. Dr. Cherny avers that a drug having greater ionophoric ability relative to a second drug would be more likely to confer greater Abeta reduction in the brain (See Paragraph 15 of Cherny Declaration). Dr. Cherny testifies that the experiment which he conducted compares the ionophoric properties of CC with 1033 and 1051 compared to a positive control compound CQ using the protocol outlined in Paragraph 18 of Cherny Declaration. The results of the experiments for each test compound is depicted in Paragraph 19, and reproduced hereinbelow.



Dr. Cherny testifies further in Paragraphs 21 and 22 of the Cherny Declaration, as follows:

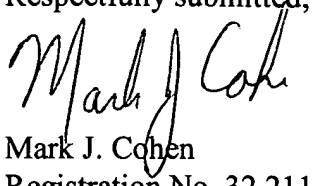
> 21. The control experiment without drug (Cu/PBS) indicated there was some uptake of copper by the cells when the test compound was absent. As shown by the data depicted in the graph above, when CQ was added, the amount of copper taken up was 0.61 μM; for CC, the amount of copper taken up was 1.18 μM; for 1051, the amount of copper taken up was 1.65 μM; and for 1033, the amount of copper taken up was 2.73 μM.
>
> 22. Thus, in the ionophore test, as described in Paragraphs 18-21 herein,1033 exhibits greater than a two-fold rise in ionophore performance over CC, while 1051 exhibits a significant rise in ionophore performance over CC. More specifically, 1033 provides a 231% rise and 1051 provides a 39.8% rise in ionophore performance, respectively relative to CC.

Dr. Cherny testifies that, in his opinion, the skilled artisan would conclude that the tests show that 1051 and especially 1033, exhibit "a significantly enhanced capability relative to CC to reduce the levels of Abeta, a common target protein of Alzheimer's disease therapies." See Paragraph 23 of Cherny Declaration.

Thus, based on the testimony of Dr. Cherny and the data in the Cherny Declaration, there is only one conclusion, i.e., PBT 1051 and especially PBT 1033, exhibit unexpected results relative to the CC compound. Accordingly, PBT 1051 and especially PBT 1033 and thus the subject matter of Claims 32 and 33 are patentable over the CC compound, a position to which Examiner Seaman concurred at the interview. Therefore, the rejection of Claims 32 and 33 under 35 U.S.C. §103 is overcome; withdrawal thereof is respectfully requested.

Thus, in view of the Declarations of Barnham and Cherny and the amendments to the claims and the Remarks hereinabove, it is respectfully submitted that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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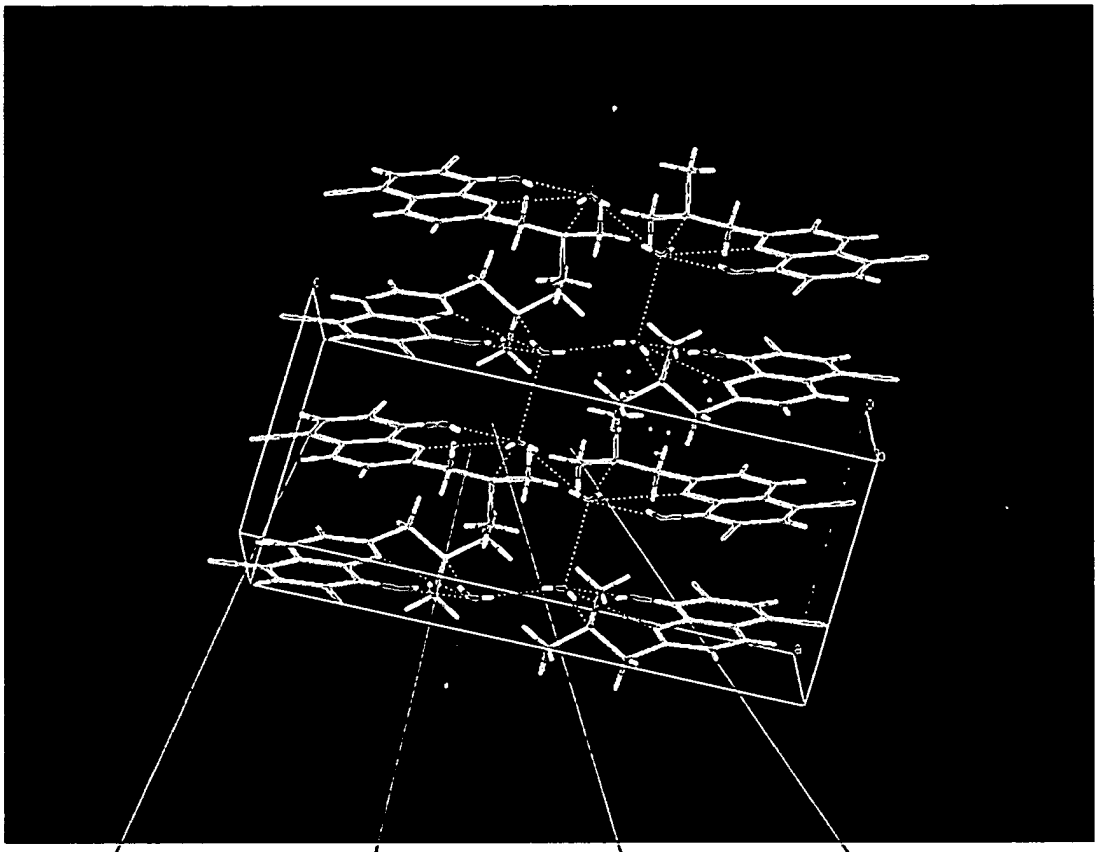
Chlorine
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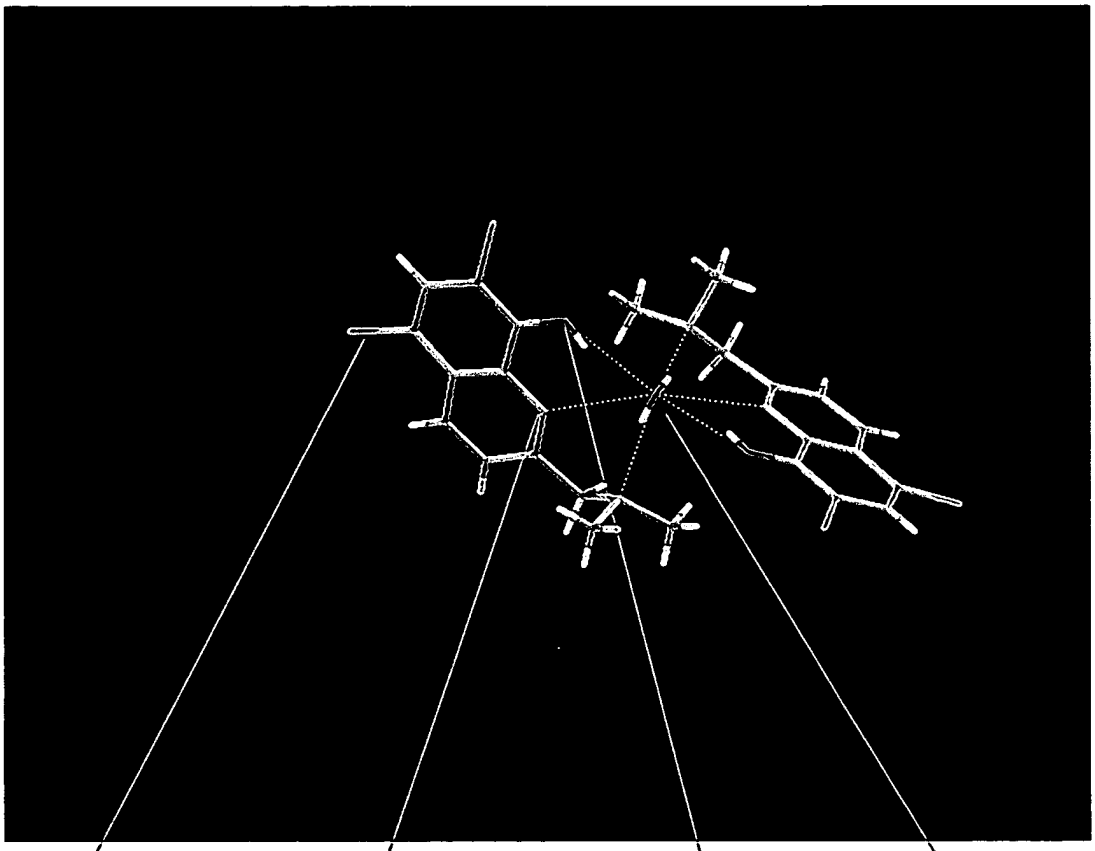
H_2O


Chlorine
Nitrogen
OH
H_2O